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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/564,481	03/07/2006	Masahiko Kuroda	2006 0025A	7350

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EXAMINER	
SALMON, KATHERINE D	
ART UNIT	PAPER NUMBER
1634	
MAIL DATE	DELIVERY MODE
10/29/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/564,481	KURODA ET AL.	
	Examiner	Art Unit	
	KATHERINE SALMON	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 July 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,10 and 11* is/are pending in the application.

4a) Of the above claim(s) *2-5,10 and 11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,6-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. It is noted that the examiner in application 10/564481 has been changed. Please direct all correspondences to Katherine Salmon, Art Unit 1634.

2. This action is in response to papers filed 7/03/2008.

3. Claims 1-8 and 10-11 are pending. Claim 9 has been cancelled.

4. Claims 2-5 and 10-11 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 2/20/2007 and made FINAL.

5. The following rejection is reiterated. Response to arguments follows.

6. This action is FINAL.

Withdrawn Objections and Rejections

7. The objection to claim 9 made in section 3 of the previous office action is moot based upon cancellation of the claim.

8. The objection to the specification made in section 4 of the previous office action is moot based upon amendments to the specification.

9. The rejection of the claims made under 35 USC 112/2nd paragraph in sections 7-8 of the previous office action is moot based upon amendments to the claims.

Affidavit or Declaration under 37 CFR 1.132

10. The Declaration under 37 CFR 1.132 filed 7/03/2008 is not sufficient to overcome the 35 USC 112/Enablement.

The declaration by Masahiko Kuroda points to a Figure A (p. 4 Section B), however, this figure was not provided in the submittal of the 37 CFR 1.132 Declaration submitted 7/03/2008. A phone call was placed to William Schmidt on 10/15/2008, a new 37 CFR 1.132 including figure A has been placed on the record (10/16/2008)

Kuroda describes the experiment performed to measure expression levels of HRF genes in menstrual blood from normal subjects and endometriosis patients (p. 2-4). Kuroda asserts that Figure A shows expression levels of HRG gene in menstrual blood from endometriosis patients much higher than from normal patients (p. 4 section B). Kuroda asserts that it is apparent that diagnosis of endometriosis is possible by measuring expression levels of HRF gene in menstrual blood (p. 4 section C).

These arguments made in the 37 CFR 1.132 have been fully considered but have not been found persuasive.

It is noted that although the Figure shows higher expression of HRF genes in menstrual blood compared to normal patients, this figure if submitted in a proper 37 CFR 1.132 would still not be persuasive to remove the 35 USC 112/Enablement as presented below. The claims are drawn to any species, as discussed below the instant specification has not provided any guidance to the association of HRF expression and endometriosis. The art as disclosed below discusses how such associations are unpredictable and vary between populations. Further, the claims are drawn to

endometriosis related diseases, which is a larger scope than the experiment as presented in the 37 CFR 1.132 declaration. Finally, the specification clearly shows that in Figures 2A and 2B teach that the expression levels for the eutopic endometrial samples and the normal samples had approximately the same expression levels, and that only some of the endometrial implants exhibited higher expression levels as compared with the normal. Since there is no significant demonstrated increase in HRF expression levels between endometrial tissue (both eutopic and implant) samples and normal tissue samples, the data indicates that is it unpredictable to use HRF expression levels from endometrial tissue as a means of determining the presence of endometriosis. The 37 CFR 1.132 declaration however, only presents data for menstruation blood in patients with endometriosis and therefore it is unclear if this population includes both eutopic and implant. Therefore the 37 CFR 1.132 is not sufficient to overcome the 35 USC 112 presented and maintained below.

Claim Rejections - 35 USC § 112 Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. The following 35 USC 112/Enablment is a reiteration of the rejection made of record in the previous office action. Response to arguments follows.

12. Claims 1 and 6-8 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art without undue experimentation (*United States v. Teletronics Inc*, 8 USPQ2d 1217 (Fed Cir. 1988)). Whether undue experimentation is needed is not based on a single factor, but rather a conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986)) and *In re Wands* 8 USPQ2d 1400 (Fed. Cir. 1988)).

The breadth of the claims and nature of the invention

Claims 1 and 6-8 are broadly drawn to methods of diagnosing any endometriosis-related disease by determining the expression level of histamine releasing factor (HRF) polynucleotide in an endometriotic tissue or menstrual blood biological sample and comparing the expression level with that in any normal biological sample, wherein a subject exhibiting a significantly higher HRF polynucleotide expression level when compared with any normal biological sample is indicative of a subject having any endometriosis-related disease or as a subject at risk thereof.

The nature of the invention not only involves determining the expression level of HRF in a sample from any subject, but also using that expression level to determine if a

subject has any endometriosis-related disease or is at risk thereof Since the specification does not provide a definition for the term "subject", the invention broadly encompasses examining any organism. Also, since the specification does not define "endometriosis-related disease", the invention broadly encompasses diseases such as cancer and infertility.

Guidance in the Specification and Working Examples

The specification teaches collecting tissue samples from 18 patients. The specification teaches that the samples were endometriosis implants, eutopic endometrium from endometrial patients and normal endometrial tissues from patients having no endometriosis (pg 24, lines 25-30). The specification and figure 1 teach that only 3 out of 5 endometriosis patients exhibited higher HRF expression levels in the implant tissue as compared to the normal tissue (pg 28, lines 3-6). Also, figure 2 demonstrates the results from northern blot analysis of HRF expression (pg 28, lines 21-26). Figures 2A and 2B teach that the expression levels for the eutopic endometrial samples and the normal samples had approximately the same expression levels, and that only some of the endometrial implants exhibited higher expression levels as compared with the normal. Since there is no significant demonstrated increase in HRF expression levels between endometrial tissue (both eutopic and implant) samples and normal tissue samples, the data indicates that is it unpredictable to use HRF expression levels from endometrial tissue as a means of determining the presence of endometriosis.

The specification does not teach examining HRF expression levels in patients with other endometriosis-related disorders. The specification does not teach examining HRF expression levels in other organisms. The specification does not teach what constitutes a normal expression level.

The unpredictability of the art, the state of the prior art, level of skill in the art

While the state of the art and level of skill in the art with regard to correlating gene expression with disease state is high, the level of unpredictability in associating any gene expression levels with a particular disease state is even higher. The level of unpredictability is demonstrated by the prior art, the post filing art, and the instant specification.

Oikawa (previously cited: Oikawa, et al. Journal of pathology, 2003; 199:318-323) teaches studying HRF expression in endometriotic implants and states that high HRF expression was observed in endometriotic implants when compared with normal endometriotic tissue and from eutopic endometriotic tissue from patients with endometriosis (pg 320, col 1, para 4). This indicates that HRF expression cannot be used to determine whether or not a subject has endometriosis since HRF level was considered high when compared with the eutopic endometriotic tissue from patients with endometriosis. In addition, Figure 2 demonstrates that only some of the endometriotic implant tissue samples had expression levels that were higher than normal (pg 321, col 1, Figure 2 and caption), indicating that simply determining the expression level of HRF in any endometriotic implant tissue samples cannot be used predictably to determine if a patient has endometriosis.

Regarding comparing expression level to controls, Cheung (Cheung et al. Nature Genetics March 2003; 33:422-425) teaches that there is natural variation in gene expression among different individuals. The reference teaches an assessment of natural variation of gene expression in lymphoblastoid cells in humans, and analyzes the variation of expression data among individuals and within individuals (replicates) p.422, last paragraph; Fig 1). The data indicates that, for example, expression of ACTG2 in 35 individuals varied by a factor of 17; and that in expression of the 40 genes with the highest variance ratios, the highest and lowest values differed by a factor of 2.4 or greater (Fig 3). Therefore, since gene expression levels can vary between individuals, it is unpredictable to use any sample as a control to perform gene expression comparisons for diagnostic purposes.

The art teaches genetic expression associations are often irreproducible. Shalon (Shalon et al. US 2001/0051344 A1 Dec 13, 2001) teaches that due to variations in genetic make-up of unrelated individuals in a heterogeneous society, differences in the expression of a gene between any two individuals may or may not be significant (see page 10, paragraph 0155). Shalon further teaches that the larger the number of individuals tested, the more significant the remaining differences in gene expression become and samples from at least 5 and preferably 20-50 different test individuals are assayed to obtain statistically meaningful data showing a statistical elevation or reduction in report levels when compared to control levels (see page 10, paragraph 0156). Shalon teaches that the test average pattern is compared with a control average pattern on a microarray to identify test genes which show significantly, typically at least

2 fold and up to 100 fold or more, increase or decrease in gene expression level with respect to control levels for the same gene (see page 10, paragraph 0158). Therefore the art teaches that genetic differences in individuals affect the expression levels of genes and make it difficult to provide a clear association between expression and disease.

Quantity of Experimentation

Claims 1 and 6-8 are broadly drawn to methods of diagnosing any endometriosis-related disease by determining the expression level of histamine releasing factor (HRF) polynucleotide in an endometriotic tissue or menstrual blood biological sample and comparing the expression level with that in any normal biological sample, wherein a subject exhibiting a significantly higher HRF polynucleotide expression level when compared with any normal biological sample is indicative of a subject having any endometriosis-related disease or as a subject at risk thereof. The specification and Oikawa teach studies of HRF gene expression in patients with endometriosis. Both studies demonstrate that HRF gene expression is not increased in endometrial tissue from endometriosis patients and they do not demonstrate a consistent or significant correlation between increased HRF gene expression in endometrial implants and endometriosis. Shalon teaches that due to variations in genetic make-up of unrelated individuals in a heterogeneous society, differences in the expression of a gene between any two individuals may or may not be significant. Shalon further teaches that the larger the number of individuals tested, the more significant the remaining differences in gene expression become and samples from at

least 5 and preferably 20-50 different test individuals are assayed to obtain statistically meaningful data showing a statistical elevation or reduction in report levels when compared to control levels. Therefore, based on the data, it is unpredictable to associate HRF gene expression level with endometriosis. Further, Shalon teaches that a study of 20-50 different test individuals would be required to obtain statistically significant data and thus the skilled artisan would be required to perform a large study in order to determine of HRF gene expression level can be predictably/significantly correlated with endometriosis. This would require undue and unpredictable experimentation with no expectation of success.

Claims 1 and 6-8 are broadly drawn to methods of diagnosing any endometriosis-related disease by determining the expression level of histamine releasing factor (HRF) polynucleotide in an endometriotic tissue or menstrual blood biological sample and comparing the expression level with that in any normal biological sample, wherein a subject exhibiting a significantly higher HRF polynucleotide expression level when compared with any normal biological sample is indicative of a subject having any endometriosis-related disease or as a subject at risk thereof. The specification does not define what constitutes an expression level in a normal biological sample. Cheung teaches that there is natural variation in gene expression among different individuals and that a study of the expression of ACTG2 in 35 individuals varied by a factor of 17. Therefore, since gene expression levels can vary between individuals, it is unpredictable to use any sample as a control to perform gene expression comparisons for diagnostic purposes. Further, the skilled artisan would be

required to perform a large study in order to determine a normal expression level, such that a change in HRF expression level could be determined. This would require undue and unpredictable experimentation with no expectation of success.

Claims 1 and 6-8 are broadly drawn to methods of diagnosing any endometriosis-related disease by determining the expression level of histamine releasing factor (HRF) polynucleotide in an endometriotic tissue or menstrual blood biological sample and comparing the expression level with that in any normal biological sample, wherein a subject exhibiting a significantly higher HRF polynucleotide expression level when compared with any normal biological sample is indicative of a subject having any endometriosis-related disease or as a subject at risk thereof.

Claims 1 and 6-8 are broadly drawn to methods of diagnosing any endometriosis-related disease by determining the expression level of histamine releasing factor (HRF) polynucleotide in an endometriotic tissue or menstrual blood biological sample and comparing the expression level with that in any normal biological sample, wherein a subject exhibiting a significantly higher HRF polynucleotide expression level when compared with any normal biological sample is indicative of a subject having any endometriosis-related disease or as a subject at risk thereof. While the claims broadly read on correlating HRF gene expression with endometriosis-related disease in any organisms, the specification and Oikawa only teach studies in humans. Disease pathogenesis can vary between organisms and therefore, it is unpredictable human data for associating gene expression with disease for diagnostic purposes in unstudied organisms.

Claims 1 and 6-8 are broadly drawn to methods of diagnosing any endometriosis-related disease by determining the expression level of histamine releasing factor (HRF) polynucleotide in an endometriotic tissue or menstrual blood biological sample and comparing the expression level with that in any normal biological sample, wherein a subject exhibiting a significantly higher HRF polynucleotide expression level when compared with any normal biological sample is indicative of a subject having any endometriosis-related disease or as a subject at risk thereof. The specification does not define endometriosis-related disease, and therefore the claims broadly read on diverse diseases such as cancer or infertility. The specification and Oikawa only teach studying HRF gene expression in patients with endometriosis. Therefore, the skilled artisan would be required to perform a large study in order to determine if HRF gene expression could be used diagnostically for other diseases. This would require undue and unpredictable experimentation with no expectation of success.

Conclusion

Given the lack of data from all organisms, the lack of significant HRF expression changes in the tissue studied, and the lack of normal expression value methods of diagnosing any endometriosis-related disease by determining the expression level of histamine releasing factor (HRF) polynucleotide in an endometriotic tissue or menstrual blood biological sample and comparing the expression level with that in any normal biological sample, wherein a subject exhibiting a significantly higher HRF polynucleotide expression level when compared with any normal biological sample is indicative of a

subject having any endometriosis-related disease or as a subject at risk thereof are replete with unpredictable experimentation that is considered undue.

Response to arguments

Applicants argue that sample from endometrial or menstrual tissue can be used diagnostically for the claimed method. This is not found persuasive, because, as described in the enablement rejection above, the disclosure does not contain any enabling subject matter.

Response to Arguments

The reply traverses the rejection. A summary of the reply is presented below with response to arguments following.

(A) The reply asserts that the specification describes the measurement of a gene in endometriosis tissue and that on p. 28 and p. 7 the specification shows that higher expression was observed in tissues of endometriosis implant (versus normal endometrial tissue and eutopic endometrial tissue from an endometriosis patient) which shows a correlation between the advancement of endometriosis and HRF expression levels (p. 8 paragraphs 2-3).

These arguments have been fully considered but have not been found persuasive.

Though the instant specification does provide assertions of an higher expression in HRF in endometriosis tissue versus normal tissue, the guidance in the specification and the art teach the unpredictability of such assertions. Figures 2A and 2B teach that the

expression levels for the eutopic endometrial samples and the normal samples had approximately the same expression levels, and that only some of the endometrial implants exhibited higher expression levels as compared with the normal. Since there is no significant demonstrated increase in HRF expression levels between endometrial tissue (both eutopic and implant) samples and normal tissue samples, the data indicates that is it unpredictable to use HRF expression levels from endometrial tissue as a means of determining the presence of endometriosis.

The reply asserts that the data shows a higher expression observed in tissues of endometriosis implant versus normal endometrial tissue and eutopic endometrial tissue from an endometriosis patient, however, the claims are not limited to such an association. Rather the claims are drawn to a higher expression in any endometrial tissue (which would include implant and eutopic endometrial tissue) versus normal tissue. Further the reply has not responded to the discussion in the 35 USC 112/Enablemtne presented above with regard to the unpredictability of extrapolating such associations between species and the broadness of the preamble which would encompass many more disorders besides just endometriosis. The term endometriosis related would further include such disorders as cancer and fertility (as discussed in the enablement above). Therefore the arguments presented in the reply have not been sufficient to remove the 35 USC 112/Enablement as presented above.

(B) The reply asserts that that with regard to expression with menstrual blood the 37 CFR 1.132 declaration confirms that HRF expression in menstrual blood is much higher in endometriosis patients (p. p. 8 4th paragraph).

These arguments have been fully reviewed but have not been found persuasive.

As discussed in the response to the 37 CFR 1.132 declaration above, the 37 CFR 1.132 declaration is insufficient to overcome the 35 USC Enablement. As noted the data presented for menstrual blood is not sufficient to overcome the enablement of record because the 37 CFR 1.132 experiment has a more narrow scope than the claimed invention. As such the declaration does not provide support for the broadness of the claims which includes any endometriosis related disorder in any species using menstruation tissue or any endometric tissue.

Conclusion

13. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to KATHERINE SALMON whose telephone number is

(571)272-3316. The examiner can normally be reached on Monday-Friday 8AM-430PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Katherine Salmon/
Examiner, Art Unit 1634

/Ram R. Shukla/
Supervisory Patent Examiner, Art Unit 1634